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FROM SYMPTOMS AND SIGNS TO DIAGNOSIS IN A RARE DISEASE, TYPE I GAUCHER DISEASE

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AbstAbstract

Gaucher disease is the most frequent lysosomal storage disease, caused by the deficiency of an enzyme called β-glucocerebrosidase. Three types of Gaucher disease are described. Type I Gaucher disease benefits from lifelong enzyme replacement therapy with imiglucerase.
Herein, we present the case of a 34-year-old female patient, a commercial worker, who was admitted to our Department of Haematology in the Emergency Clinical Hospital of Constanta in order to investigate the aetiology of a persistent splenomegaly. Clinical examination and laboratory testing evidenced the following: splenomegaly, hepatomegaly, anaemia, leukopenia and neutropenia, thrombocytopenia, and a myelogram showing Gaucher cells. In this context, the suspicion of Gaucher disease was raised and the investigations were further completed through specific enzyme testing and genetic testing. The low values of lysosomal enzymes, coupled with the detection of two specific genetic mutations confirmed the diagnosis of Gaucher disease.
In January 2017, treatment with 2400U of imiglucerase in intravenous perfusion every two weeks was begun.
Keywords: *lysosomal storage disease, glucocerebrosidase, Gaucher's cells, imiglucerase.*

Rezumat
Boala Gaucher este cea mai frecventă boală lizozomală produsă de deficitul unei enzime numită β-glucocerebrozidază. Se descriu trei tipuri de boală Gaucher. Boala Gaucher tip I beneficiază de tratament substitutiv enzimatic cronic cu imiglucerasum.
Se prezintă cazul unei paciente în vârstă de 34 de ani, de profesie lucrător comercial, care s-a internat în compartimentul de hematologie al SCJU Constanţa în iulie 2016 pentru stabilirea etiologiei unei splenomegalii. Clinic şi paraclinic s-au evidenţiat: splenomegalie, hepatomegalie, anemie, leucopenie cu neutropenie, trombocitopenie, medulogramă cu celule Gaucher. În acest context s-a ridicat suspiciunea de boală Gaucher şi s-au completat

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investigaţiile cu determinări enzimatice specifice şi teste genetice. Valorile scăzute ale enzimelor lizozomale şi detecţia a două mutaţii genetice specifice au confirmat diagnosticul de boală Gaucher.
În ianuarie 2017 s-a început tratamentul cu imiglucerasum în perfuzie intravenoasă la fiecare două săptămâni în doză de 2400U/perfuzie.
***Cuvinte cheie**: boală lizozomală, glucocerebrozidază, celule Gaucher, imiglucerasum.*

Introduction

Gaucher disease is a metabolic autosomal recessive transmitted disease that occurs due to mutations in a gene located on chromosome 1 that encodes the enzyme glucocerebrosidase. This enzyme is found in lysosomes and has the role of decomposing glucosylceramides into glucose and ceramide. Enzyme deficiency results in the accumulation of undigested metabolic substrate in lysosomes from macrophages spread throughout the body. These macrophages are called Gaucher cells and replace healthy cells especially in the spleen, liver and bone marrow. The disease has a multi-organ character. Depending on the age at its onset, clinical picture and evolution, three types of Gaucher disease are described:

1. Type I - chronic, adult or non-neuropathic form;
2. Type II - infantile, neuropathic, acute;
3. Type III - infantile, neuropathic, subacute.

Gaucher disease type I benefits from chronically enzymatic substitution treatment with imiglucerase, an enzyme obtained by recombined DNA technology. A disadvantage of chronic enzymatic therapy is the need for intravenous infusions every two weeks and the high cost of the product[1].

Presenting the case

We present the case of a 34-year-old female patient, a commercial worker, who was admitted to our Department of Haematology in the Emergency Clinical Hospital of Constanta in order to investigate the aetiology of a persistent splenomegaly.
Personal pathological history of the patient - insignificant. From the anamnesis we noted: 12 years ago, during pregnancy, moderate splenomegaly and low platelet counts were found.
Because of the lack of symptomatology, the patient did not come to the doctor until 6

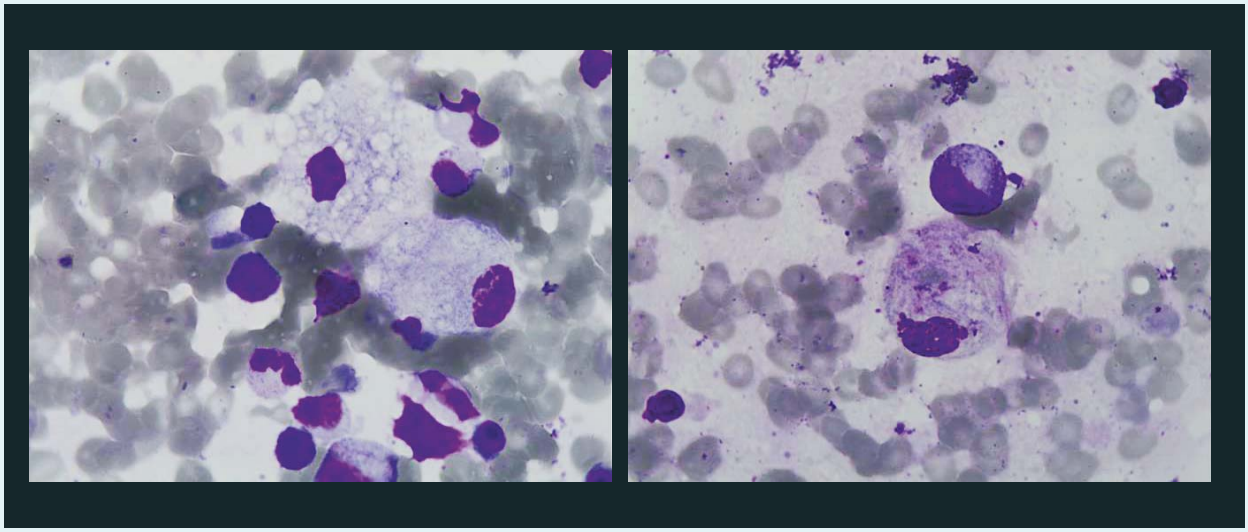

Image no. 1: *Large macrophage, relatively small eccentric nucleus, cytoplasm abundant fibrillary aspect ("crepe paper / onion sheets"), and sometimes containing vacuoles.*

Bone segment	T score	Z score	BMD
Lumbar spine	-2.4	-2.4	0.778 (N: 1.05 ± 0.15)
Right thigh -bone	-0.8	-0.7	0.830 (N: 1.05 ± 0.15)
Left thigh -bone	-0.4	-0.2	0.890 (N: 1.05 ± 0.15)

Table no. 1. *Osteodensitometry*

months ago when abdominal pain, fatigue during medium labour and sporadic pain in the lumbar spine and lower limbs appeared. Until admission to the haematology department, the patient consulted three different specialists about her symptomatology: family doctor, internist and surgeon.

The objective exam at admission highlighted: good general condition, afebrile; body constitution: H=175 cm, W=63Kg, BMI=20,6 kg/m^2; without cutaneous-mucosal haemorrhagic syndrome, without external lymph nodes; hepatomegaly: the right lobe with the lower margin at 3cm below the midclavicular line; splenomegaly with the lower spleen of the spleen at 15 cm below the coastal rebord. Laboratory examinations revealed: Hb = 9,9g/ dl; Leukocytes no. = 2150/ mm^3, Neutrophils = 1130/ mm^3; Platelets no. = 69.000/ mm^3; MCV = 91 fl; MCH = 29 pg; Reticulocytes = 112000/ µL; Serum iron = 90γ/ dl. The renal and hepatic triage samples were within normal range. Viral markers and HIV test were negative.

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Abdominal ultrasound: Liver enlarged overall. VP = 14,6 mm. Normal structure and size of pancreas. Spleen- D1 = 95 mm, D2 = 284 mm, D3 = 75 mm; spleen volume = 670 mm^3.
Bone marrow examination (aspirated): frequent Gaucher cells with cytoplasmic fibrillary appearance, diffuse distribution (image no.1).

Osteomedular biopsy
Histopathological: the haematogenous marrow compactly occupies medullary spaces, but cellularity is represented by 60% Gaucher-type histiocytes; preserved haematopoietic area with the slightly diminished presence of all series.
Immunohistochemical: Gaucher cells express diffuse CD68/KP1 (histiocytic marker).
Osteodensitometry sacral lumbar region and bilateral hip – table no.1
The BMD values (0.778) and the T score values (-2.4) at the level of the lumbar spine pleads for osteopenia. Moderate fracture risk. The BMD values (0.830) and the T score values (-0.8) at the level of the right thigh-bone neck pleads for normal values. Reduced fracture risk. The BMD values (0.890) and the T score values (-0.4) at the level of the left thigh-bone neck pleads for normal values. Reduced fracture risk.
Native MRI and IV contrast agent MRI - sections in the coronary area of the femur and bilateral calf. Changes in bone imaging compatible with Gaucher disease. (image 2 and image 3)

Positive diagnosis

In this clinical and laboratory testing context, namely splenomegaly, hepatomegaly, anaemia, leukopenia with neutropenia, thrombocytopenia, Gaucher cell myelogram, the suspicion of Gaucher disease was raised and the investigations were completed with specific enzymatic determinations and genetic tests. The values of lysosomal enzymes were as follows:

- beta – glycosidase = 0 (VN=200-2000 pmol/spot*20h)
- beta – galactosidase = 0.16 (VN= 0.5 – 3.2 nmol/spot*21h)

Genetic tests detected two heterozygous mutations: c.1226A>G and c.115+1G>A
The low values of lysosomal enzymes, coupled with the detection of two specific genetic mutations confirmed the diagnosis of Gaucher disease.

Treatment and evolution

In December 2016 the CNAS approval for the enzymatic substitution therapy with imiglucerase. Therefore, in January 2017 the treatment with imiglucerase in intravenous perfusion begun once every two weeks with the dose of 2400U/ perfusion, under

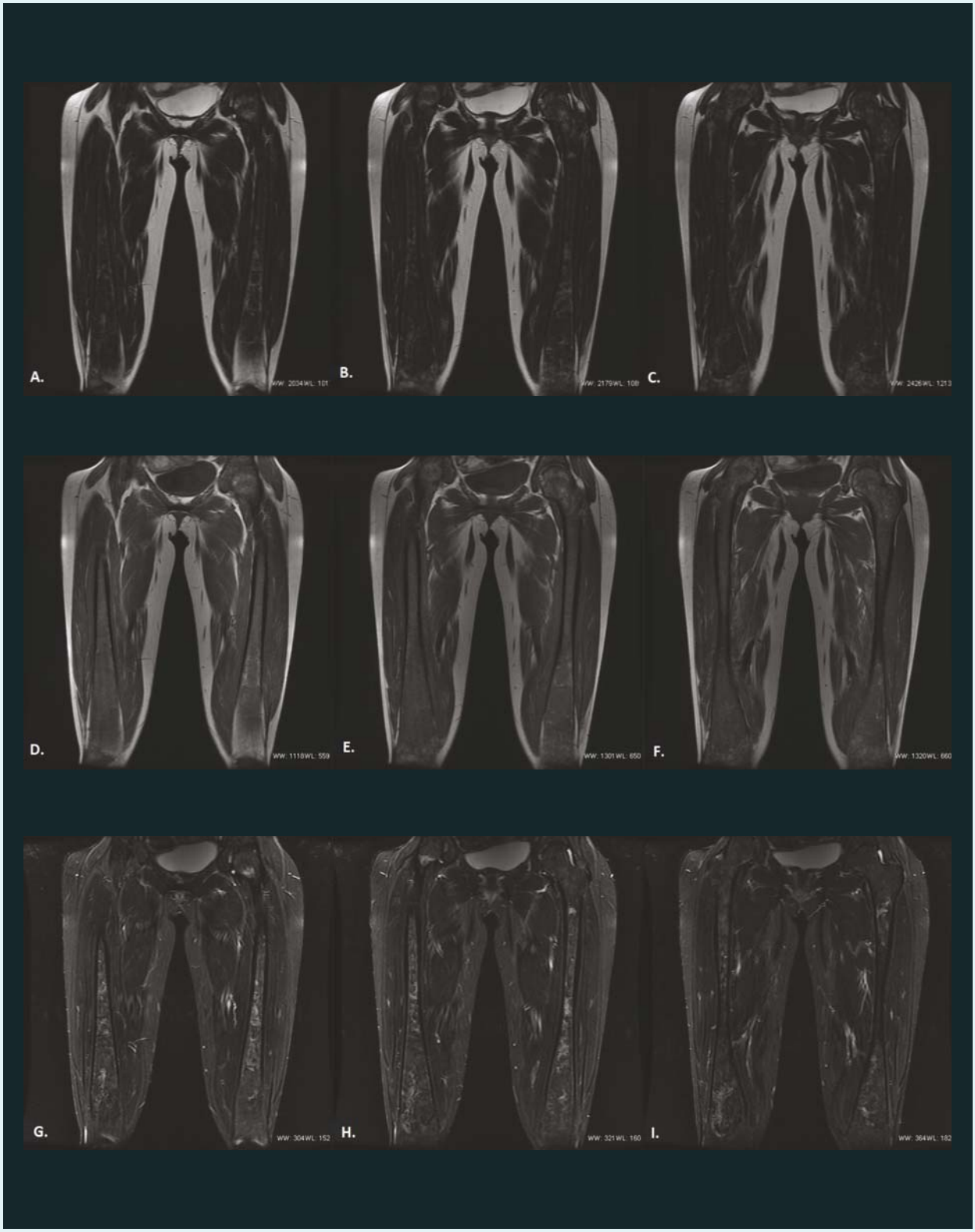

Image no. 2 *Gaucher disease: Düsseldorf score 8, the severity class of bone marrow infiltration IIa.*
Bone MRI: sections in the coronary femur area T2 (A, B, C), T1 (D, E, F) and STIR (G, H, I); small, focal, inframillimetric areas, slightly hyposignal T1- hypersignal T2; bilateral intramedular STIR hypersignal with a non-homogeneous contrast setting; femoral diaphysis deformation (1/2 distal) Erlenmeyer balloon type, with cortical integrity.

permanent clinical and haematological control. In monitoring the patient, we will consider the following objectives:

- clinically: reducing the spleen volume by 30-50% and the liver volume by 20-30% after the first year of enzyme replacement therapy;
- laboratory tests: the haemoglobin should increase after the first year of treatment at ≥11g/dl and the platelets at least 1.5 times their initial value.

Discussions - conclusions

When the patient was presented we discussed and excluded outcomes and conditions that evolve with hepato-splenomegaly, anaemia and thrombocytopenia.

1. Hepatic cirrhosis: absence of clinical and laboratory analysis signs of hepatic failure and portal hypertension and viral markers.
2. Chronic lymphoproliferative syndrome / lymphoma: absence of superficial and profound adenopathy, normal leukocyte formula and subsequently absence of medullary infiltration.

After bone marrow examination, enzymatic determinations and genetic tests, we excluded disorders with other lipid storage abnormalities such as Niemann-Pick disease or Pompe disease. Bone marrow examination may contribute to the differential diagnosis of Gaucher disease but cannot fully confirm the diagnosis. Positive diagnosis requires confirmation by enzymatic and molecular tests. Enzyme tests show glucocerebrosidase enzyme deficiency, and molecular DNA analysis the structural gene defects[2]. A 2007 study on a group of 98 patients from the USA and 38 patients from Australia and New Zealand revealed that the average duration since the first signs or symptoms suggestive of Gaucher disease up to diagnosis was 49 ±124 months for the USA group and 36±73 months for the Australia and New Zeeland group. The patients saw up to 8 different specialists (on average 3.0 ± 1.2) related to their condition: internists, paediatricians, haemato-oncologists, orthopaedists, gastroenterologists, geneticists, neurologists, gynaecologists, rheumatologists. [3] In this case, the average duration from the first signs and symptoms until the diagnosis was 144 months, the patient first consulted with three different specialists (family physician, internist, surgeon). Splenomegaly is present in 90% of patients, and anaemia, thrombocytopenia and, to a lesser extent, leukopenia can be observed simultaneously or independently of each other.[4,5] In this case, the anaemia, thrombocytopenia and leukopenia were present at the same time. The balloon Erlenmeyer type deformation of the femur, also present in our case, occurs in approximately 30-45% of adults with Gaucher disease, but so far, no link has been

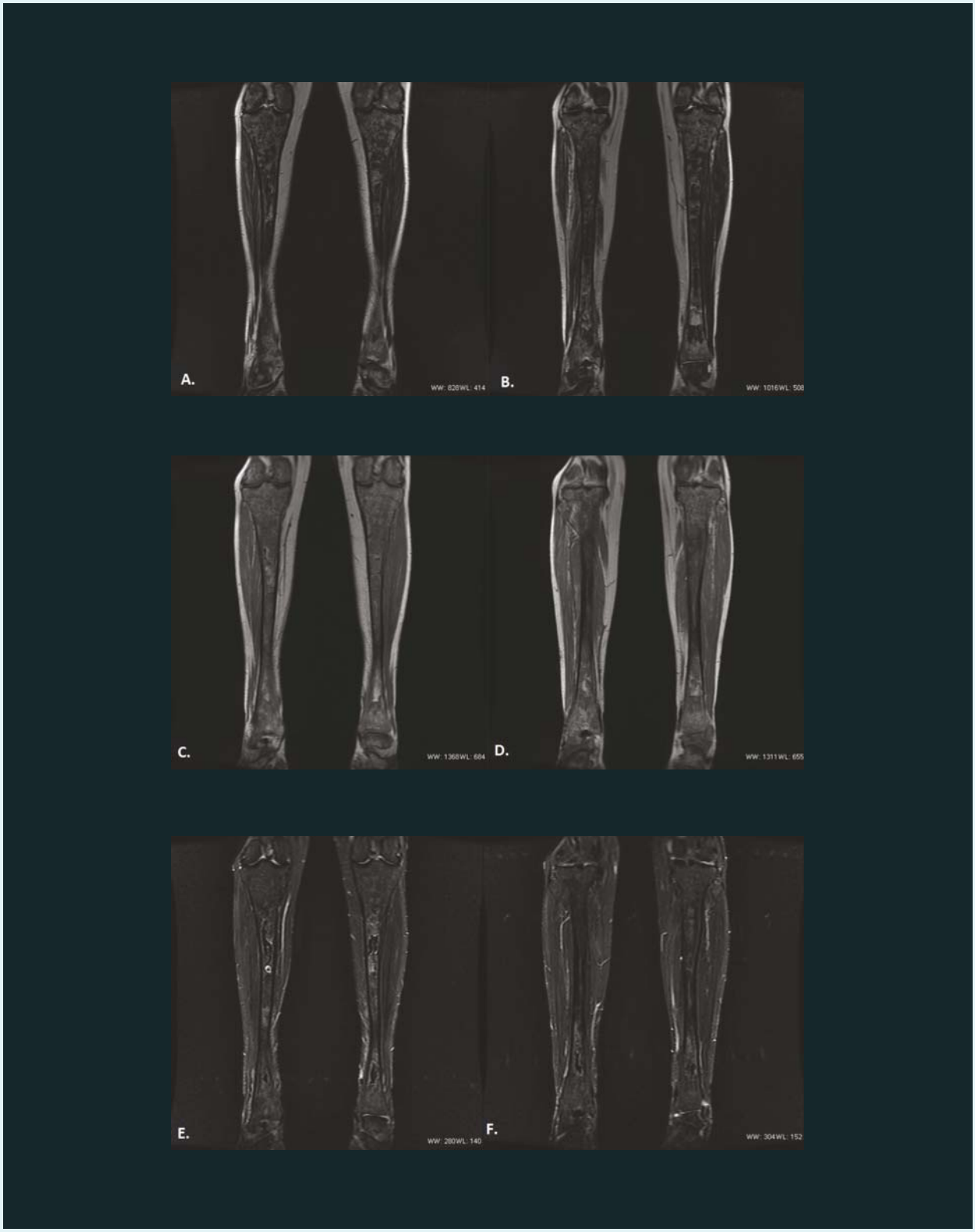

Image no. 3 *Gaucher disease: Düsseldorf score 8, the severity class of bone marrow infiltration IIa.*
Bone MRI: sections in the coronary bilateral calf area T2 (A,B), T1 (C, D) and STIR (E, F); small, focal, inframillimetric areas, slightly hyposignal T1 - hipersignal T2; bilateral intramedular STIR hypersignal with a non-homogeneous contrast setting.

established between this radiological discovery and other musculoskeletal complications of the disease.[6] Although musculoskeletal manifestations in Gaucher disease do not correlate with the severity of the disease, they significantly contribute to morbidity and disability.[7] Necrosis of femoral heads, femoral condyles or femoral plateaus are typical bone lesions in Gaucher disease. Acute pain (bone crisis), signs of local inflammation and fever may suggest an infection. These can take several days or weeks. Radiographies after stabilization of lesions may reveal avascular necrosis or bone infarction.[8] Enzyme replacement therapy virtually eliminated the need for splenectomy, which is associated with pulmonary hypertension, sepsis, advanced liver disease, and rapid progression of bone disease.[9] Enzymatic substitution treatment cannot reverse hepatic, splenic, or medullar fibrosis. Thus, early treatment is important before the development of irreversible complications.[10] The result rates for the therapeutic target may vary depending on the organ or system. Visceral and haematological compartments may begin to respond within 12 months of treatment, achieving the therapeutic target between 12 and 36 months.[11]

Particularity of the case

Long duration, 144 months, from the first signs and symptoms suggestive of Gaucher disease to the time of diagnosis. During this period, the patient was in activity with normal work schedule.

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